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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/774,903	02/10/2004	Nnochiri N. Ekwuribe	9233.74CT	8777

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EXAMINER	
RUSSEL, JEFFREY E	

ART UNIT	PAPER NUMBER
1654	

DATE MAILED: 07/22/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/774,903	EKWURIBE ET AL.	
	Examiner	Art Unit	
	Jeffrey E. Russel	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 February 2004 and 10 May 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *50-68* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *50-68* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *10 February 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *13 sheets*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

1. Applicants are requested to check the spelling of the first name of inventor Ramaswamy. It is spelled differently in the Transmittal Letter than in the declaration. If necessary, Applicants should file a request for corrected filing receipt.

2. In the priority claim inserted by the preliminary amendment filed February 10, 2004, the status of parent application 09/336,548 should be updated, and the status of parent application 10/018,879 should be updated when it finally issues.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 62-65, 67, and 68 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The conjugates of the formulas recited in claims 50 and 66 do not comprise any lipophilic groups. Compare, e.g., page 7, lines 1-2 and 10-11, and the formulas at page 8, lines 6-19, and in originally-filed claim 1; and see also the definitions of the variable "o" at, e.g., page 8, line 15, and page 9, line 8. The specification states that a conjugate not comprising any lipophilic group occurs only after the conjugate comprising the lipophilic group is administered in vivo, at which point the PEG lipophile bond is hydrolyzed, leaving the insulin/drug-PEG compound to circulate in the blood. See, e.g., page 7, lines 20-26; and see also page 10, lines 12-16, cited by Applicants as support for the new claim language. Accordingly, there is no original disclosure of the conjugates of claims 50 and 66 in the form of a pharmaceutical composition in

combination with a pharmaceutical carrier, nor is there any original disclosure of the administration of the conjugates of claims 50 and 66 not comprising any lipophilic groups. Rather, pharmaceutical compositions and pharmaceutical carriers are only disclosed in conjunction with conjugates comprising lipophilic groups, and the administration of conjugates is limited to conjugates comprising lipophilic groups.

4. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 50-54, 56-61, and 66 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 49-60 of U.S. Patent No. 6,309,633. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the '633 patent anticipate the instant claims. In particular, when the drug-oligomer conjugates of Formula 1 are administered to a subject as set forth in claims 49-60 of the '633 patent, inherently the hydrolyzable bonds will be hydrolyzed, resulting in a drug conjugated to hydrophilic bonds with the same structure as is recited in the instant claims.

5. The effective filing date of instant claims 50-61 and 66 is deemed to be June 19, 1999, the filing date of parent application 09/336,548. Instant claims 50-61 and 66 are deemed to be

entitled under 35 U.S.C. 120 to the benefit of the filing date of the '548 application because the '548 application, under the test of 35 U.S.C. 112, first paragraph, discloses the claimed invention.

Instant claims 62-65, 67, and 68 are not deemed to be entitled under 35 U.S.C. 120 to the benefit of the filing date of parent application 10/018,879 because the '879 application, under the test of 35 U.S.C. 112, first paragraph, does not disclose pharmaceutical compositions comprising conjugates not comprising lipophilic groups and comprising pharmaceutical carriers, and does not disclose the administration of conjugates not comprising lipophilic groups.

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

For the purposes of this invention, the level of ordinary skill in the art is deemed to be at least that level of skill demonstrated by the patents in the relevant art. Joy Technologies Inc. v. Quigg, 14 USPQ2d 1432 (DC DC 1990). One of ordinary skill in the art is held accountable not only for specific teachings of references, but also for inferences which those skilled in the art may reasonably be expected to draw. In re Hoeschele, 160 USPQ 809, 811 (CCPA 1969). In addition, one of ordinary skill in the art is motivated by economics to depart from the prior art to reduce costs consistent with desired product properties. In re Clinton, 188 USPQ 365, 367 (CCPA 1976); In re Thompson, 192 USPQ 275, 277 (CCPA 1976).

7. Claims 50-54, 62, and 64 are rejected under 35 U.S.C. 102(b) as being anticipated by Borgman (U.S. Patent No. 5,536,743) as evidenced by Thornfeldt et al (U.S. Patent No. 5,723,114). Borgman teaches a pharmaceutical composition for intravaginal administration comprising Oleth-3 and water. See column 18, Example 4. Oleth-3 corresponds to Applicants' drug-oligomer conjugate in which the oligomer is polyethylene glycol comprising an average of 3 PEG units, and oleyl alcohol corresponds to Applicants' drug. Thornfeldt et al (see, e.g., claims 5, 10, and 20) is cited as evidence that oleyl alcohol is a drug, i.e. it is an epithelial penetration enhancer. The ether bond joining the polyethylene glycol and the oleyl alcohol is a non-hydrolyzable bond.

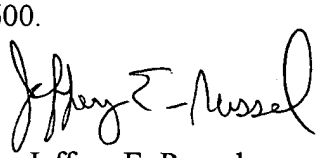
8. Claims 50, 54-57, 62, and 64 are rejected under 35 U.S.C. 103(a) as being obvious over Zalipsky (U.S. Patent No. 5,612,460). Zalipsky teaches polyethylene glycol conjugated through urethane/carbamate bonds to the amino groups of proteins. The polyethylene glycol can comprise as few as 10 PEG units, and the PEG terminus which is not conjugated to the protein can be a hydroxy group. The conjugates are to be used therapeutically. See, e.g., the Abstract; column 1, lines 16-27; column 2, lines 11-22; column 3, lines 46-64; and column 5, lines 1-7. Zalipsky does not teach the specific combination of a polyethylene glycol comprising 10 PEG

units and with a hydroxy group terminus. It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to form conjugates according to Zalipsky in which the polyethylene glycol comprises 10 PEG units and has a hydroxy group terminus because these individual variations are disclosed to be useful by Zalipsky, because polymer length is an art-recognized result-effective variable which is routinely determined and optimized by one of ordinary skill in the art and is a variable which Zalipsky discloses the need to optimize, and because the use of a hydroxy group rather than a methoxy group at the terminus of a relatively small PEG would have been expected to increase the solubility of the resulting conjugate.

9. Claims 58, 63, and 65-68 are rejected under 35 U.S.C. 103(a) as being obvious over Zalipsky (U.S. Patent No. 5,612,460) as applied against claims 50, 54-57, and 62 above, and further in view of Davis et al. Zalipsky teaches conjugation to proteins in general, but does not teach conjugation to an amino group of insulin in particular. Davis et al teach the desirability of conjugating PEG to proteins such as insulin via amino groups present in the insulin. See, e.g., column 3, line 45 - column 4, line 9; Examples X-XII; and claims 1-13. It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to conjugate the polyethylene glycol suggested by Zalipsky as discussed in the above paragraph with insulin because Zalipsky is not limited to any particular proteins, and because Davis et al teach the desirability of conjugating PEG to insulin in particular.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey E. Russel at telephone number (571) 272-0969. The examiner can normally be reached on Monday-Thursday from 8:30 A.M. to 6:00 P.M. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Bruce Campell can be reached at (571) 272-0974. The fax number for formal communications to be entered into the record is (571) 273-8300; for informal communications such as proposed amendments, the fax number (571) 273-0969 can be used. The telephone number for the Technology Center 1600 receptionist is (571) 272-1600.



Jeffrey E. Russel

Primary Patent Examiner

Art Unit 1654

JRussel

July 19, 2005